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Reply to the Editor:

We appreciate the thoughtful comments that Cantinotti and colleagues expressed in their letter. Cantinotti and colleagues are to be commended for their important body of work, which has advanced the understanding of B-type natriuretic peptide (BNP) levels in pediatric patients with congenital heart disease.[1]

We agree that levels of BNP are age dependent both in healthy neonates and in those with congenital heart disease. Also, as we indicated in the recent article under discussion,[2] the rapid changes in BNP levels after surgical intervention (within hours of the operation) imply that there are physiologic changes associated with the specific surgical interventions because of the particular underlying cardiac defects that determine the release of BNP. Indeed, neonates with univentricular physiology have very high preoperative BNP levels relative to those of age-matched healthy neonates and also relative to those with left-to-right shunts. In our study, there was also a trend toward higher BNP levels in neonates with univentricular physiology relative to those undergoing an arterial switch operation. We believe this is one reason that studies grouping neonates into single cohorts,[3,4] without consideration for the specific cardiac defects, have not found the postoperative decreases in BNP that both we[2] and Cantinotti and colleagues[1] found.

We therefore caution against relying on disease severity scoring systems that group diverse cardiac defects within particular categories or combine various diagnostic criteria, such as the Risk Adjustment for Congenital Heart Surgery 1 and Aristotle Basic Complexity scores, for the interpretation of perioperative BNP levels. Indeed, these scoring systems do not fully account for the variability in outcomes seen, demonstrating that other factors remain important.[5] In attempting to understand better the physiologic release of a biomarker and its implications for prognostication and goal-directed therapy, the use of such scoring systems is therefore likely to fall short in accounting for the variability in levels of the biomarker. In fact, in Figure 1 of the letter of Cantinotti and colleagues, neonates in Aristotle Basic Complexity categories II and III can be seen to have more variability in BNP levels than those in category IV, probably because of the differences in cardiac lesions and the physiologic changes associated with surgery that inherently differ by category in these systems. A further example of the specificity we described in our study was shown in preliminary data from our previous work, where we found that *preoperative* BNP level in patients undergoing a total cavopulmonary connection (Fontan procedure) was the only significant predictor of adverse postoperative outcomes.[6]

There is clearly much to learn about the mechanisms involved in BNP release in patients with congenital heart disease and the utility of this biomarker in this population. We agree with Cantinotti and colleagues that further investigations into BNP changes during the perioperative period are warranted. On the basis of our combined data to date, we believe that fully understanding and interpreting perioperative BNP changes will require accounting for age, the cardiac lesion, and the intervention that is undertaken. We thank both the Editor and Cantinotti and colleagues for this opportunity to highlight this important topic.

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TRACHEAL REGENERATION: MYTH OR FACT?

To the Editor:

We read with great interest the article entitled, ‘‘Tracheal regeneration: Evidence of bone marrow mesenchymal stem cell involvement,’’ by Seguin and coworkers.[1] We congratulate Seguin and coworkers[1] for their convincing demonstration of bone marrow–derived stem cell migration to the grafted area after tracheal replacement

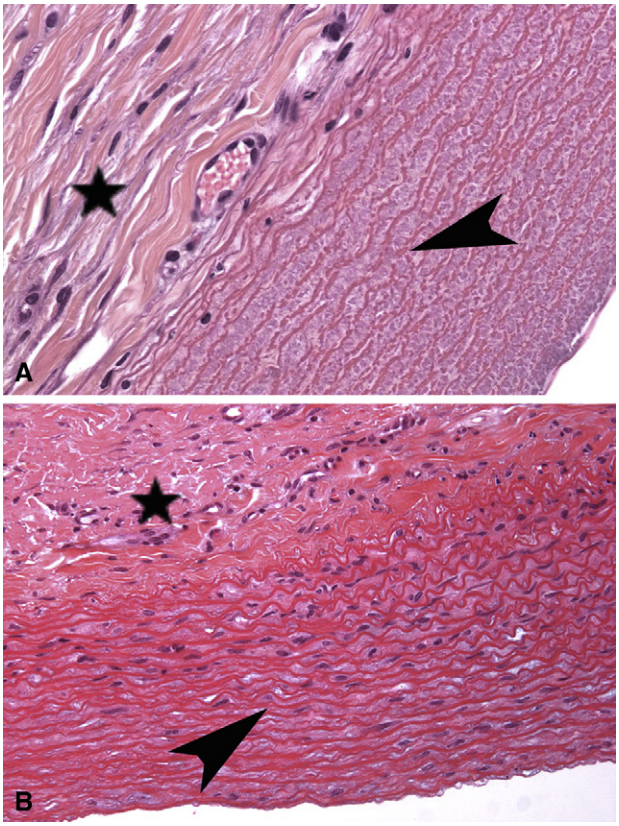

FIGURE 1. A, Pathologic examination of a fascial flap–wrapped fresh allogeneic aorta after insertion of a too-wide polyethylene tube, showing a necrotic aortic graft circumference (*arrowhead*) characterized by the evanescence of smooth cells into the elastic fiber network (hematoxylin eosin and saffron stain, original magnification 200×). B, By comparison, fascial flap–wrapped fresh allogeneic aorta after an adequate tube insertion, showing a viable aortic graft circumference (*arrowhead*; hematoxylin eosin and saffron stain, original 200×). *Black stars* indicate the surrounding fascia.

with an aortic allograft in a New Zealand rabbit model. In the same model, we previously investigated the revascularization process in both fresh and cryopreserved thoracic aortic allografts after fascial wrap in a heterotopic position and then the construction of an aortic graft–based tracheal substitute.[2,3] Our preliminary anatomic studies discovered a significant discrepancy between the tracheal and thoracic aortic inner diameters (approximately 6 mm and 4 mm wide, respectively), and we first attempted to solve this issue by forced insertion of a 4.8-mm wide polyethylene tube, increasing the aortic graft diameter and maintaining a patent lumen during the revascularization period. Unfortunately, this overdistention invariably led to graft necrosis (Figure 1), characterized by evanescence of smooth cells into the elastic fiber network of the aortic wall and inconsistent calcification deposits (unpublished data). Given the need for forced insertion of a 5-mm diameter stent supporting the aortic allograft in Seguin and coworkers' study,[1] we would like to know whether such necrotic lesions as described here were observed in the aortic graft tissue of animals that died or were killed at less than 1 month. We hypothesize that such a necrotic scaffold, containing only residual elastic fibers, makes regeneration of mature tracheal tissue improbable aside from nonspecific epithelial cell ingrowths.[1] The presence of bone marrow mesenchymal stem cells in the grafted area could result in their capacity for nonspecific migration and homing toward different kinds of damaged or injured tissues.[4] As stated by Seguin and coworkers,[1] only islands of nascent cartilage were shown in close proximity to anastomoses. The origin of these cartilaginous islets, however, remains elusive because of the negative results for Y chromosome detection. Furthermore, the relevance of these cartilaginous islets was not explored, because animals surviving longer than a year did not have any attempt at removing the stent to prove a successfully regenerated or remodeled airway. These disappointing results contrast with confirmed tracheal regeneration in allogeneic aortic grafts observed after the landmark investigations of long tracheal replacements in sheep and minipig models,[5,6] which in fact were all conducted on juvenile animals (continuing their growth even though sexually mature). One might hypothesize that such a favorable outcome could result from the high level of secretion of growth hormone, which directly stimulates tissue regeneration and chondrocyte multiplication.

In fact, the mesenchymal stem cell mobilization to the graft area and cartilaginous islets shown here are more in line with clinical results in the long-term follow-up (mean, 70 months) of our aortic allograft–grafted adult patients,[7] who currently still require stenting and therefore show no evidence of actual clinically relevant tracheal remodeling into the graft.

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Reply to the Editor:

We read with interest the comments addressed by Wurtz and coworkers on our article, ''Tracheal regeneration: Evidence of bone marrow stem cell involvement.''[1] We greatly appreciate their congratulations for having provided a ''convincing demonstration of bone marrow–derived stem cell migration to the grafted area after tracheal replacement with an aortic allograft in a New Zealand rabbit model.'' More generally, we thank them for their strong support to our pioneering experimental works,[2-5] which led to the first human applications.[6,7] Nevertheless, we would like to discuss some key points arising from their letter.

In our rabbit model, we observed a radically different evolution of the aortic graft. To answer precisely their comments, neither necrosis nor overdistention of the thoracic aorta by the endoprosthesis occurred in our experiments. A stent of 5 mm in diameter was inserted with moderate distention of the aorta so that the elastic tissue would not collapse. As shown in Figure 1 of the original article, stent and aortic dimensions matched well with the cervical tracheal diameter after graft interposition. Moreover, as underlined by our article, stent migration was one of the main complications, proving that the stenting has not been forcefully made. Perhaps age and weight of the rabbits in Wurtz and coworkers' experimentations were not properly chosen? We are also surprised by the polyethylene tube they reported using in their unpublished studies. In our sheep and human work, we paid great attention to base our studies on a tracheal prosthesis that had already been evaluated in clinical applications, and we decided to use a flexible pediatric tracheal silicone stent (Tracheobronxane Dumon; Novatech, La Ciotat, France).

Finally, did Wurtz and coworkers observe such necrosis both with and without stenting in their model? The real difference that we want to underline is the allotransplantation site of the aorta. Also, a muscle flap could be a better option than a fascial flap to promote revascularization. This has been clearly demonstrated in our experimental and clinical work on airway transplantation with aortic allografts.[7,8]

We completely agree with Wurtz and coworkers that ''the presence of bone marrow mesenchymal stem cells in the grafted area could result in their capacity for nonspecific migration and homing toward different kinds of damaged or injured tissues.'' As they have noted, we constructed our experimentations on the basis of mesenchymal stem cell circulating theory, hypothesizing that injured rabbits would use circulating mesenchymal stem cells to avoid bone marrow mobilization.[9] It is well known that unspecific mesenchymal stem cells migrate to inflammatory sites attracted by the liberation of chemokines on the place of injury. The real challenge is to find the other triggers orienting these cells to secondly differentiate to obtain tracheal regeneration.

We disagree with Wurtz and coworkers, however, who would compare these uncompleted results on the rabbit model with the first human applications, in which cartilage regeneration seems to be delayed. The structure of the human aorta is histologically closer to the aorta of the minipig than to the aorta of the rabbit. There is still hope to get similar results to those observed in these experimentations with cartilage regeneration. We are still working on multiple hypotheses to explain the delayed regeneration of human cartilage, such as patient age (older meaning no circulating growth factor), sex influence (more often men than women), tumoral pathology, previous impairing treatments (chemotherapy), and so on.

To conclude, the myth turned into reality with the first demonstration of tracheal regeneration in animal studies at the beginning of our experience.[2-4] Today, the main issue is to obtain the same regenerative processes in human beings. A prospective study (TRACHEOBRONC-ART trial) is in progress at our center to confirm not only the feasibility of airway transplantation with cryopreserved aortic allograft but also the possibility of airway regeneration in human beings.

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